Characterization of the functional relevance of genetic variants identified in genome wide association studies on intracranial aneurysm

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Research question and background

Subarachnoid hemorrhage (SAH) from a ruptured intracranial aneurysm (IA) is a subset of stroke that occurs at a relatively young age (mean age 50 years) and has a poor prognosis (a third of the patients dies from the consequences of SAH). IAs develop most frequently on the arteries of the circle of Willis, a circle of arteries at the base of the brain. The pathogenesis of IA development and rupture is largely unknown. Recent genome wide association studies (GWAS), identifying six loci strongly associated with IA, show that a genetic predisposition is involved.
To better understand the genetics of this disease, it will be crucial to characterize the functional relevance of the genetic varants identified in these GWAS loci. All SNPs (single nucleotide polymorphisms) identified in the GWAS for IA are located in non-coding regions and recent studies show that most disease- and trait-associated SNPs are located in or close to enhancer regions. Furthermore, my own analysis of the IA GWAS identified loci, using existing information on genome organization, shows that most of the SNPs are in close proximity to putative enhancer regions. Therefore, I hypothesize that the IA associated SNPs affect the expression of thus far unknown candidate genes by influencing enhancer activity.

Methods and tissues used

To test this hypothesis we have performed chromatin immunoprecipitation techniques to identify putative enhancers. For this experiment we used human circle of Willis tissue from the Netherlands Brain Bank, because the identification of these enhancers is tissue dependent. Therefore it was crucial to obtain human circle of Willis material. Furthermore we have performed chromosome conformation capture assays to identify putative target genes of the putative enhancers that we found. At the moment we are using in situ hybridization techniques to further investigate the putative target genes that we identified.

Results and conclusion

We have identified 38 putative enhancers in the GWAS loci using chromatin immunoprecipitation techniques. We tried to identify putative target genes of these enhancers using chromosome conformation capture assays. This has resulted in a few putative candidate genes that we are now investigating further using in situ hybridization techniques. We cannot draw any conclusions yet on which enhancers and genes might be involved in the pathogenesis of IA.